18. (Amended) The nucleic acid of claim 13, wherein the antigenic peptides are from non-structural proteins.

REMARKS

Claims 1-30 are pending in this application. Claims 1-12 and 20-30 have been withdrawn from consideration as being drawn to a non-elected invention. Claims 13-19 are currently under examination. Claims 14 and 15 have been canceled. Claim 13 has been amended to recite the limitations of Claim 15. In addition, Claims 13 and 16 has been amended to correctly recite the invention. Claims 16 and 18 have been amended to correctly recite their dependency from Claim 13. The specification is amended herein to recite a priority claim to a previously filed application. The corrected sequence listing, submitted herewith, corrects an inadvertent typographical error to SEQ ID NO:55 as it was originally filed with the International PCT application. Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "Version with markings to show changes made." No new matter is believed added. Support for these amendments, if needed, can be found throughout the specification as set forth below. In particular, support for corrected SEQ ID NO:55 can be found in Figure 3 as modified vector/pCV3 correctly recites "ctggttccgc gtggatcgca gcgaattctc gaggatccat ccggccgca tcgtga" (SEQ ID NO:55 as filed in the PCT application incorrectly recites "ctggttccgc gtggatcgca gcgaattctc gaggatccat cc**c**ggccgca tcgtga"). Support for amendment of Claim 13 to recite "antigenic peptides from the same

domains," rather than homologous, can be found in Figure 18 and in Example 3 (page 23, line 18 to page 30, line 23) and elsewhere throughout the specification. Support for amendment of Claim 16 to recite NS4, rather than nucleocapsid proteins, can be found in Figures 18-20, in Example 3 (page 23, line 18 to page 30, line 23) and elsewhere throughout the specification.

The enclosed diskette contains the corrected Sequence Listing for this application in computer readable form (CRF). A paper copy of the corrected Sequence Listing in compliance with 37 C.F.R. §§ 1.821-1.825 is also enclosed. Applicants hereby certify that the information in the computer readable form on the diskette and in the hard copy of the Sequence Listing enclosed herewith is the same and includes no new matter.

In light of the following remarks, Applicants respectfully request reconsideration of this application and allowance of the pending claims to issue.

I. Rejections under 35 U.S.C. § 112

Claims 13-19 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Specifically, it is alleged that Claim 13 is vague and indefinite in the recitation of "homologous antigenic peptides." Further, the Examiner alleges that the specification fails to teach what level of homology is required in order to determine that peptides of different sequences belong to different genotypes or subtypes of a species.

Applicants submit that the amendment of Claim 13 to incorporate the limitations of original claim 15 and cancellation of Claim 14 overcome this rejection. Specifically, the limitation of the claims to nucleic acids encoding peptides from the same domains from different genotypes of HCV render the claims definite as the different genotypes of HCV and what differentiates one genotype from another are well-known to those of skill in the art. Applicants therefore respectfully request removal of this basis of rejection.

Claims 13 and 14 are rejected under 35 U.S.C. § 112, first paragraph, for allegedly failing to fulfill the "written description" requirement. Applicants submit that the amendment of Claim 13 to incorporate the limitations of original claim 15 and cancellation of Claim 14 render this basis moot. Applicants therefore respectfully request removal of this basis of rejection.

Claims 13 and 14 are rejected under 35 U.S.C. § 112, first paragraph, for the alleged failure of the specification to reasonably provide enablement for nucleic acids encoding mosaic proteins comprising antigenic peptides from different genotypes from any species other than HCV.

Applicants submit that after amendment of Claim 13 to recite the same claim limitations as original Claim 15 and cancellation of Claim 14, all remaining claims recite mosaic proteins made from antigenic peptides from different genotypes of HCV. Applicants submit that the

Examiner has acknowledged that such mosaic proteins are reasonably enabled by the specification as filed. Consequently, Applicants respectfully request removal of this basis of rejection.

II. Rejections under 35 U.S.C. § 102

a) Claims 13 and 14 are rejected under 35 U.S.C. § 102(b) as being anticipated by Khudyakov et al. (*J. Virology* 68: 7067-7074 (1994)). Khudyakov et al. allegedly teaches a synthetic gene encoding a mosaic protein comprising antigenic peptides from different strains of hepatitis E virus.

Applicants submit that amendment of Claim 13 to recite the same claim limitations as original Claim 15, specifically that the plurality of peptides is from different genotypes of hepatitis C virus, renders amended Claim 13 patentable over Khudyakov et al. as original Claim 15 was found by the Examiner to be patentable over Khudyakov et al. Further, Applicants submit that cancellation of Claim 14 renders the rejection of that claim moot. Applicants respectfully request removal of this basis of rejection.

b) Claims 13 and 14 are rejected under 35 U.S.C. § 102 (b) as being anticipated by Fields et al. (*Clin. Diagnos. Virol.* 5: 167-179 (1996)). Specifically, it is alleged that Fields et al. teaches a synthetic gene encoding an artificial mosaic protein comprising antigenic peptides of more than

one strain of HEV.

Applicants submit that amendment of Claim 13 to recite the same claim limitations as original Claim 15, specifically that the plurality of peptides be from different genotypes of hepatitis C virus, renders amended Claim 13 patentable over Fields et al. as original Claim 15 was found by the Examiner to be patentable over Fields et al. Further, Applicants submit that cancellation of Claim 14 renders the rejection of that claim moot. Applicants respectfully request removal of this basis of rejection and allowance of remaining claims to issue as amended.

c) Claims 13-16 are rejected under 35 U.S.C. § 102 (a) as allegedly being anticipated by Ruedinger et al. (Abstracts of the 97th General Meeting of the American Society for Microbiology, abstract #V-54 (May 4-8, 1997)). This rejection is moot as to cancelled Claim 14.

Applicants note that the present application relies for priority on U.S. Patent application Serial No. 08/921,887, which was filed August 25, 1997, less than one year after the March publication date of Ruedinger et al. Also, the cited reference is the inventors' own publication. This reference lists co-authors not listed as co-inventors and is properly cited. Applicants include herewith a Katz-type Declaration, as Exhibit A, which describes the contribution of each of the non-inventor co-authors to the research described in Ruedinger et al.

Specifically, the Declaration under 37 C.F.R. § 1.132 by co-author and co-inventor Dr. Yury Khudyakov states that neither Birgit Ruedinger nor Chih-Wei Chang had any role in the conception of the claimed invention. Therefore, Birgit Ruedinger and Chih-Wei Chang are not co-inventors of the presently claimed invention. Thus, Ruedinger et al. does not represent a disclosure of the claimed invention by "others." Applicants therefore request that it be removed as a 35 U.S.C. § 102(a) reference, and that the present basis for rejection be withdrawn.

d) Claims 13-14 are rejected under 35 U.S.C. § 102(e) as being anticipated by Fields et al. (U.S. Pat No. 5,563,032). Specifically, it is alleged that Fields et al. teaches a nucleic acid encoding an HEV mosaic protein comprising regions from more than one strain.

Applicants submit that amendment of Claim 13 to recite the same claim limitations as original Claim 15, specifically that the plurality of peptides be from different genotypes of hepatitis C virus, renders amended Claim 13 patentable over Fields et al. as original Claim 15 was found by the Examiner to be patentable over Fields et al. Further, Applicants submit that cancellation of Claim 14 renders the rejection of that claim moot. Applicants respectfully request removal of this basis of rejection and allowance of remaining claims to issue as amended.

III. Rejections under 35 U.S.C. § 103

Claims 13-16 and 18 are rejected under 35 U.S.C. § 103 (a) as allegedly being

unpatentable over Khudyakov et al., in view of Zhang et al., Bukh et al. and Chien et al. Specifically, the Examiner alleges that it would have been *prima facie* obvious for one of ordinary skill in the art at the time the invention was made to have made a synthetic gene for recombinant expression of a mosaic protein comprising immunodominant epitopes of the HCV core and/or NS proteins based on the sequence information provided by Zhang et al. and Bukh et al. according to the methods described by Chien et al. Furthermore, it is alleged that one of ordinary skill in the art at the time the invention was made would have been motivated to express the mosaic protein for use as an immunoassay reagent to detect HCV genotypes other than genotype 1a or 1b with greater sensitivity, as is allegedly suggested by Khudyakov et al.

In making a determination of obviousness under 35 U.S.C. § 103, the Examiner must establish a prima facie case that (1) the prior art suggests the invention developed, and (2) the prior art indicates that the invention would have a reasonable likelihood of success. In re Dow Chem. Co., 837 F.2d 469, 5 U.S.P.Q.2d 1529 (Fed. Cir. 1988); In re Geiger, 815 F.2d 686, 2 U.S.P.Q.2d 1276 (Fed. Cir. 1987).

Further, in respect to (1) above, when a rejection is based on a combination of references, the references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination. In evaluating whether the references provide this suggestion, the use of hindsight is impermissable. Thus, the PTO can satisfy its burden of

establishing a prima facie case of obviousness "only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references." In re Fine, 837 F.2d 1071, U.S.P.Q.2d 1596 (Fed.Cir. 1988). It is axiomatic that this burden is not fulfilled if it is merely obvious to try the claimed combination.

Applicants submit that references cited do not provide the required motivation to combine the references as is outlined in the following:

Khudyakov et al. provides no motivation for its combination with the other cited references to provide the present invention. Specifically, it provides no motivation to combine the references for the purpose of creating nucleic acids that encode a mosaic protein containing more than one antigenic peptide from the same domain from different genotypes of HCV.

Khudyakov et al. teaches an HEV mosaic comprising more than one antigenic polypeptide from the same domains from different variants of HEV. There is no suggestion that this teaching can or should be applied to generate analogous HCV mosaic proteins or polypeptides. Rather, Khudyakov et al. cites the work of Chien et al. in a way that teaches away from the making of an HCV mosaic protein. Khudyakov et al. refer to Chien et al. (reference 9; last paragraph, page 7072) as illustrating a potential solution to the problem of detecting

different strains of HEV that were not entirely solved by use of the HEV mosaic protein. As such, by reference to Chien et al. (see below), Khudyakov et al. suggest a chimeric (non-mosaic) HEV protein made by the method of Chien et al. Furthermore, as it only describes how the principles of Chien et al. may be applicable for producing an improved HEV protein, Khudyakov et al. neither teaches nor suggests any HCV protein, much less a mosaic HCV protein. Therefore, there is no motivation in Khudyakov et al. to combine its teaching regarding HEV with any reference related to HCV. Applicants therefore request removal of Khudyakov et al. as a basis for this ground of rejection under 35 U.S.C. § 103.

Zhang et al. provides no motivation for its combination with the other cited references to provide the present invention. Specifically, it provides no motivation to combine the references for the purpose of generating any nucleic acid that encodes a mosaic protein containing antigenic epitopes of HCV. Rather, Zhang et al. provides significant motivation not to generate a mosaic HCV protein. In particular, Zhang et al. teaches the use of a panel of 16 type-specific synthetic peptides to detect the presence of antibodies specific for HCV. When presented as separate entities in an array, these different type-specific antigens effectively provide the goals sought by Zhang et al. Specifically, the assay provides a high level of sensitivity to diverse strains of HCV and an ability to identify which strains are present . As recited in the last sentence of the abstract, "(t)he major advantage of using four different antigenic regions is that we often obtain high absorbance values which are easily interpreted, or multiple reactions which confirm each

other." This major advantage, and others as described by Zhang et al., are only possible when the different antigens are not fused together in a mosaic protein as is the case in the present invention (see abstract). As such, Applicants submit that Zhang et al. teaches against its combination with any other reference that teaches fusing together antigenic regions to form mosaic proteins. Thus, the combination of Zhang et al. with Khudyakov et al. is inappropriate, as a combination of antigenic sequences in a mosaic polypeptide (e.g., of Khudyakov et al.) would eliminate what is viewed by Zhang et al. as the primary advantages of their array. In addition, the significant success described by Zhang et al. in generating an effective assay for detection and typing of HCV provides no motivation for one of skill in the art to attempt to create other, very different, assays. Applicants request removal of Zhang et al. as a basis for a ground of rejection under 35 U.S.C. § 103.

Bukh et al. provides no motivation for its combination with the other cited references to provide the present invention. Bukh et al. teaches the complete sequence of the core gene of 52 different HCV isolates. However, there is no teaching that these sequences should be combined for any purpose. Rather, in light of the potential problems relating to then-current genotyping systems, certain other, very different, approaches to provide improvements are suggested. Specifically, Bukh et al. recognizes the problem of potential false-negatives, "(d)espite the high degree of conservation in the immunodominant regions... heterogeneity of the C protein could lead to false-negatives in current serological tests" (page 8243, 1st full paragraph). Bukh et al.

also proposes solutions to the stated problem. The first solution is the use of different antigens that have sequences conserved across the different genotypes, "...most isolates of genotypes 3 and 4 ha(ve) an identical amino acid sequence at positions 65-81..." However, if this is not adequate to provide a suitable assay, Bukh et al. proposes an even more definitive approach in stating, "...sequence analysis of gene regions that are predictive of genotype may be necessary for a definitive determination" (page 8243, bottom of 2nd full paragraph). While Bukh et al. teach sequences of some HCV genotypes, it provides motivation and guidance to use this information in a way that does not suggest the present invention. In fact, by explicitly suggesting certain approaches as preferred, Bukh et al. teach away from the present claims, which recite a significantly different approach. Therefore, Applicants request removal of Bukh et al. as a basis for a ground of rejection under 35 U.S.C. § 103.

Chien et al. provides no motivation for its combination with the other cited references for the purpose of creating nucleic acids encoding polypeptides derived from different HCV genotypes. Specifically, it teaches the fusion of selected epitopes from different regions of a single HCV genotype, HCV-1, to form a single polypeptide which is also reactive with other genotypes of HCV. This provides no motivation or teaching with regard to any mosaic-encoding nucleic acid. In fact, this non-mosaic approach was deemed by Chien et al. to be successful without any modification. As indicated in the abstract, "...this anti-C25 assay detects all previously identified HCV-seropositive cases..." Applicants therefore submit that there was no

motivation in Chien et al. to attempt further development of improved assays in general, and no specific motivation to make any mosaic polypeptide-based assay. Further, given that Khudyakov et al. specifically points to the approach taken by Chien et al. as a promising alternate approach to generate a better HEV diagnostic than the HEV mosaic (see above), there was no reason at the time of the invention to even believe that an HCV mosaic would be as good as the HCV chimera taught by Chien et al. Accordingly, there could be no motivation for one of skill in the art to generate a mosaic protein comprising antigenic peptides from different genotypes of a hepatitis C virus. Rather, the teaching of Chien et al. in any circumstance is to generate only a chimeric protein comprising portions of the polyprotein of a single genotype. Chien et al. teaches away from the mosaic approach taught by Khudyakov et al. for HEV, and thus, teaches against combining its teaching with Khudyakov et al. Applicants therefore submit that this reference teaches away from the present invention. Applicants request removal of Chien et al. as a basis for this ground of rejection under 35 U.S.C. § 103.

In summary, Applicants submit that the burden of the PTO to establish a prima facie case of obviousness has not been met as the references as a whole do not suggest the desirability of making the combination as outlined in the Office Action. In fact, in each reference cited, there are specific teachings against the combination of references used to support the alleged obviousness. For example, summarizing the arguments made above; Khudyakov et al. suggests that chimeric proteins are likely preferable to mosaic proteins, Zhang et al. suggests the

desirability of not combining antigens to form polypeptide mosaics, Bukh et al. suggests abandonment of protein-based diagnostics if it is not possible to find epitopes which are adequately cross-reactive across all genotypes, and Chien et al. indicates that there is no need to find further HCV antigens for diagnostic purposes. Further, Applicants submit that the approach of Chien et al. in generating an antigenically-reactive protein is similar to that of Bukh et al. in that it seeks to identify specific regions of a single genotype which are cross-reactive with many different genotypes. As such, Applicants submit that one of skill in the art, using the teachings of these references as a whole, would not apply the methods of Chien et al. to generate a mosaic protein, even if there was an acknowledged shortcoming in the chimeric protein of Chien et al.

Thus, Applicants submit that these references, both individually and in any foreseeable combination which takes into account the references as a whole, all teach away from the present invention. Therefore, Applicants request removal of Chien et al. as a basis for a ground of rejection under 35 U.S.C. § 103 and request allowance of pending claims to issue.

Pursuant to the above amendments and remarks, consideration and allowance of the pending application is believed warranted. The Examiner is invited and encouraged to directly contact the undersigned if such contact may enhance the efficient prosecution of this application to issue.

No additional fees are believed to be warranted; however, the Commissioner is hereby authorized to charge any fees which may be required to Deposit Account No. 14-062.

Respectfully submitted,

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I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, Washington, D.C. 20231, on the date shown below.

Gwendolyn D. Spratt — 12-10-01

Gwendolyn D. Spratt — Date

Marked-Up Version Showing Changes Made

In the Claims:

13. (Amended) A nucleic acid encoding a mosaic protein, wherein the mosaic protein comprises a plurality of [homologous] antigenic peptides from the same domains from different genotypes of [a species] hepatitis C virus.

16. (Amended) The nucleic acid of Claim 13 [15], wherein the antigenic peptides are from NS4 [nucleocapsid] proteins.

18. (Amended) The nucleic acid of Claim 13 [15], wherein the antigenic peptides are from non-structural proteins.